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Handgrip strength – a risk indicator for type 2 diabetes: systematic review and meta-analysis of observational cohort studies

Running Title: Handgrip strength and type 2 diabetes

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Abstract

Aims: Evolving debate suggests that handgrip strength (HGS), a measure of muscular strength, might be associated with the risk of type 2 diabetes (T2D); however, the evidence is conflicting. Using a systematic review and meta-analysis of published observational cohort studies in general populations**,** we aimed to assess the association of HGS with the future risk of T2D.

Methods: Relevant studies were sought from inception until April 2020 in MEDLINE, Embase, Web of Science, and manual search of relevant articles. Transformed or extracted relative risks (RRs) with 95% confidence intervals (CIs) comparing the top vs bottom thirds of HGS levels were pooled using random effects meta-analysis.

Results: A total of 10 unique observational cohort studies comprising of 177,826 participants and >5,167 T2D cases were eligible. The pooled multivariable RR (95% CI) for T2D comparing the top vs bottom thirds of HGS levels was 0.73 (0.63-0.84). This association was consistent across several relevant subgroups except for evidence of effect modification by sample size (*p*-value for meta-regression<0.001): evidence of an association in smaller studies (< 250 events) 0.50 (0.40-0.63), with no significant association in bigger studies (≥ 250 events) 0.87 (0.73-1.05). There was no evidence of small study effects using formal tests such as funnel plots and Egger's regression symmetry test.

Conclusion: Pooled analysis of observational cohort studies suggests that HGS may be a risk indicator for T2D in the general population. The role of utilizing handgrip strength measurements in T2D prevention strategies warrants further investigation.

Systematic review registration: PROSPERO 2020: CRD42020181434

KEYWORDS

handgrip strength; type 2 diabetes; cohort studies; meta-analysis

1. INTRODUCTION

Diabetes and its complications pose a major global public health threat.[1] Diabetes mellitus in all forms is the ninth major cause of death.[2] Globally, 1 in 11 adults have diabetes mellitus, of whom 90% have type 2 diabetes (T2D).[1] Older age, obesity, family history of T2D, genetic and lifestyle factors such as physical inactivity, smoking, unhealthy diet and excessive alcohol are major risk factors for T2D. Although, established risk factors explain a large proportion of T2D risk, identification of individuals at elevated risk of T2D still constitutes a difficult undertaking, as a significant amount of residual risk remains to be fully ascertained. This suggests a need to identify and investigate putative risk factors that may have both predictive and causal relevance for T2D and could aid in the development and implementation of newer therapeutic and preventive strategies.

There is established evidence on the role of regular physical activity in promoting physical fitness and reducing the incidence of chronic disease as well as mortality risk.[3,4] Physical fitness is one of the strongest predictors of individual future health status[5] and has cardiorespiratory fitness (CRF) and muscular fitness as its main components;[5] with muscular fitness comprised of muscular strength, muscular endurance and muscular power.[5] The inverse and independent relationship between CRF and vascular disease and mortality, and its ability to predict these outcomes is well established.[6-9] Handgrip strength, widely adopted as a proxy for muscular strength[10,11] and a measure of physical fitness, has also emerged as a strong risk indicator for adverse health outcomes. Several prospective studies have demonstrated HGS to be inversely and independently associated with vascular and non-vascular disease, as well as mortality outcomes.[12-17] High HGS reflects the ability to participate in regular muscle-strengthening activities and also physical activity which increases or maintains CRF, which may prevent morbidity and mortality by having beneficial effects on resting metabolic rate, adipose tissue, blood glucose levels, insulin response and sensitivity, and blood pressure levels.[5] Emerging data suggests that HGS may also be related to T2D; however, the evidence so far has been inconsistent. Some studies have

shown inverse associations between HGS and T2D,[18-21] whereas other studies have demonstrated no evidence of an association.[22,23] A number of these studies have also been based on cross-sectional and case-control designs, which do not provide evidence of temporality. A previous review attempted to synthesize the evidence on the association between muscular strength (handgrip strength) and T2D;[24] however, it included studies with a mix of exposures – HGS alone, muscular strength assessed in both the upper and lower body, as well as total body muscular strength. Given that there is evidence suggesting that HGS may not always be a proxy for overall muscle strength,[25,26] whether a prospective relationship exists between HGS specifically and risk of T2D needs evaluation. Given the uncertainty in the evidence, our aim was to assess the nature and magnitude of the association of HGS with the risk of T2D using a systematic review and meta-analysis of available published observational cohort studies.

2. MATERIALS AND METHODS

2.1 Data sources and searches

This review which was registered in the PROSPERO prospective register of systematic reviews (CRD42020181434) was based on a predefined protocol and conducted in accordance with PRISMA and MOOSE guidelines [27,28] (**Tables S1-S2**). We searched MEDLINE and Embase from inception to 21 April 2020 with no restrictions placed on language. The computer-based searches used a combination of key words or terms relating to the exposure ("handgrip strength", "muscular strength") and outcome ("type 2 diabetes"). The full search strategy is reported in **Table S3**. One author (SKK) screened titles and abstracts of retrieved citations to assess their suitability for potential inclusion, followed by acquisition of full texts for detailed evaluation. Full text evaluation was independently conducted by two authors (SKK and NMI). The reference lists of relevant studies and review articles were manually scanned for additional studies and citing references were also checked in Web of Science.

2.2 Eligibility criteria

The protocol was pre-specified to include general population-based observational cohort (retrospective or prospective, case cohort, or nested case-control) studies if they had at least 1 year of follow-up and examined the relationship of HGS with the risk of incident T2D in adult patients. The following studies were excluded: (i) case-control study designs and (ii) those in individuals with pre-existing history of diabetes.

2.3 Data extraction and quality assessment

One author (SKK) initially extracted relevant data from eligible studies using a predesigned data collection form and a second author (NMI) independently checked the data with that in original articles. Data were extracted on (i) study design characteristics (geographical location, year of enrolment, study design, sample size, and follow-up); demographic characteristics (age, sex); exposure assessment; and outcomes (number of T2D events and the most fully-adjusted relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) of outcomes (and corresponding 95% confidence interval [CIs]). When there were multiple publications involving the same cohort, study selection was limited to a single set of most comprehensive results to avoid double counting of study participants in the pooled analysis. The key criterion used for selection was the most up-to-date comprehensive study (longest follow-up or analysis covering the largest number of participants). Methodological quality of studies was assessed using the nine-star Newcastle–Ottawa Scale (NOS),[29] which uses pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. Nine points on the NOS reflects the highest study quality.

2.4 Statistical analyses

The summary measure of association was presented as a RR with 95%CI. Hazard ratios and odds ratios were assumed to approximate the same measure of RR based on the rare disease assumption and that

reported HRs are constant across the follow-up period.[30] To enable a consistent approach to the meta-analysis, enhance pooling and interpretation of the results, reported study-specific risk estimates were transformed to comparisons involving the top versus bottom tertiles of HGS values using standard statistical methods, [31,32] which have been described in previous reports.[33,34] For comparisons that could not be transformed, the extreme groups as reported (ie, maximum versus minimal value of HGS) were used for the analyses, described previously.[4] This methodology utilised in a previous review[4] is considered reliable as we have shown that pooled estimates from transformed and untransformed data are qualitatively similar.[35] When the highest HGS was the referent, we converted the reported risk estimate into its reciprocal. Risk estimates were pooled using a random effects model to minimize the effect of between-study heterogeneity.[36] Between study statistical heterogeneity was quantified using standard chi-square tests and the I^2 statistic.[37] To determine the degree of heterogeneity, we also estimated 95% prediction intervals which provide a region in which about 95% of the true effects of a new study are expected to be found.[38,39] Pre-specified study-level characteristics such as geographical location, sex, average age at baseline, average duration of follow-up, number of cases, and methodological quality were explored as sources of heterogeneity, using stratified analysis and random effects meta-regression.[40] We also assessed the potential for small study effects such as publication bias through formal tests, namely Begg's funnel plots[41] and Egger's regression symmetry test.[42] All statistical analyses were performed using Stata version MP 16 (Stata Corp, College Station, Texas).

3. RESULTS

3.1 Study identification and selection

The selection of eligible studies is illustrated in **Figure 1**. We retrieved 87 relevant articles from the search of the databases and manual screening of relevant articles. Following screening of titles and abstracts, 18 citations were eligible for full text evaluation. Following evaluation, 8 articles were excluded because: (i) exposure was not relevant (n=3); (ii) study design not relevant (n=2); (iii) population not

relevant (n=2); and (iv) based on a review (n=1). In aggregate, we included 10 articles representing 10 unique observational cohort studies comprising of 177,826 general population participants (including > 5,167 T2D events).[20,23,43-50]

3.2 Study characteristics and quality

Table 1 summarises baseline characteristics of the eligible studies evaluating the associations between HGS and T2D. Publication years ranged from 2007 to 2019 and all the studies were based on prospective cohort designs. The average age at baseline ranged from approximately 37.0 to 74.0 years, with a weighted mean (SD) of were 51.0 (4.5) years. Except for two studies which enrolled only male or female participants, the rest enrolled both males and females. Five studies were based in North America (Canada and USA); two in Europe (Switzerland and UK); one was multinational (17 countries); and one each in Asia (Japan) and the Pacific (Australia). Average duration of follow-up ranged from 4.0 to 19 years, with a weighted mean (SD) of 4.7 (2.2) years. Though there was slight variation in the degree of covariate adjustment, all studies adjusted for at least four conventional risk factors for T2D such as age, sex, body mass index (BMI), smoking status, alcohol consumption, family history of diabetes, physical activity, or prevalent hypertension. Overall methodological quality scores of studies ranged from 7 to 9 (**Table 1 and Table S4**).

There was considerable variation in tools and methods of assessing HGS across studies; the Jamar hand-held dynamometer appeared to be commonly used among studies (**Table 2**). Three studies reported HGS as weight normalised values.[20,46,49] The majority of studies defined T2D as stated by the American Diabetes Association (ADA) based on a fasting plasma glucose of ≥7 mmol/l (126 mg/dl) (**Table 2**). Additional definitions included glycated haemoglobin ≥6·5% (48 mmol/mol), self-reported physician diagnosis, and use of antidiabetic medications.

3.3 Handgrip strength and risk of T2D

The pooled fully-adjusted RR (95% CI) of T2D comparing the top versus bottom third of HGS values was 0.73 (0.63 to 0.84) (**Figure 2**). The 95% prediction interval for the pooled RR was 0.48 to 1.12%, which is the range for the true RR for any new single study. There was substantial heterogeneity between the contributing studies (I^2=74%, 51 to 86%; p<0.001). Little of the heterogeneity in the contributing studies was explained by differences in several study level characteristics other than study size (p for meta-regression<0.001); smaller studies (number of T2D events < 250) reported a decreased risk of T2D, whereas there was no evidence of an association in bigger studies (number of T2D events ≥ 250) (**Figure 3**).

Several sensitivity analyses were conducted to test the robustness of the observed association. Exclusion of any single study at a time from the meta-analysis did not change the direction of the association, yielding pooled RRs (95% CIs) which ranged from 0.69 (0.56-0.86) to 0.79 (0.70-0.88) (**Figure S1**). On exclusion of all three studies that used weight normalised HGS as an exposure, the RR (95% CI) of T2D comparing the top versus bottom third of HGS was 0.70 (0.52-0.93).

3.4 Publication bias

Though subgroup analysis suggested there might be evidence of selective reporting, a funnel plot of the 10 studies reporting on the associations between HGS and the risk of T2D showed no evidence of asymmetry (**Figure S2**), which was consistent with Egger's regression symmetry test (p=0.21).

4. DISCUSSION

Though abundant evidence suggests an independent association between HGS and risk of vascular events, the relationship between HGS and T2D has been uncertain. In this meta-analysis of 10 population-based prospective cohort studies, increased HGS was associated with a lower risk of T2D. The inverse

association remained robust and significant in several sensitivity analyses. Subgroup analyses using clinically relevant study-level characteristics suggested that the association might be modified by the sample size, i.e., there was a tendency for smaller studies to report positive findings (small study effects); however, our formal tests for small study effects showed no evidence of this bias. In a previous effort to aggregate existing data on the relation between HGS and T2D, Tarp and colleagues pooled 13 studies that evaluated the association between CRF, muscular strength and the risk of T2D and demonstrated that a 1 SD higher muscular strength was associated with a 13% lower risk of T2D. [24] Whereas they included studies with different measures of HGS which did not enhance consistency, our evaluation specifically evaluated HGS as an exposure.

Potential mechanisms for decreased risk of T2D in individuals with high levels of HGS have been postulated. The protective effect of higher HGS on vascular disease may be mediated by reduction in incidence of weight gain, abdominal adiposity, insulin resistance, and inflammation.[5] Hence, given that CVD and diabetes share common risk factors such as BMI, physical activity, smoking, and inflammatory markers such as C-reactive protein, similar pathways may underlie the relationship between HGS and T2D. Resistance training, which is an effective way of increasing HGS, is able to increase muscle mass and strength, thus reducing visceral fat deposition and improving insulin sensitivity and glycaemic control.[51] Handgrip strength is an indicator of frailty,[11] which is often associated with fatigue, reduced muscle mass, and high susceptibility to chronic diseases such as CVD and T2D. These observational findings could also be attributed to reverse causality i.e., diabetes could be associated with lower HGS. Indeed, in a bi-directional Mendelian randomization study to assess the effect of markers of muscle mass and strength on diabetes and glycaemic traits, Yeung and colleagues demonstrated that increased grip strength could be related to lower diabetes risk and conversely showed diabetes to be associated with lower grip strength.[52] Diabetes may directly contribute to muscle loss, frailty or functional disability leading to lower HGS via dysglycaemia; insulin resistance; inflammatory processes; impairment of

skeletal muscle, mitochondrial function, and bio-energetic capacity; comorbidities such as CVD and obesity; and mechanisms linked to decreased cardiopulmonary reserve and restricted physical movement.[53-55]

The association between elevated HGS and decreased T2D risk has clinical implications. Assessment of HGS may represent an important approach for T2D prevention, for instance in the areas of screening of individuals at risk of T2D, recommending lifestyle modification, as well as further diabetes management strategies. We have recently shown that information on HGS augments CVD mortality risk prediction beyond that of traditional risk factors and that it may be potentially suitable for population-level risk assessment.[16] Handgrip strength may be a potential risk assessment tool in general or specialized clinical settings to identify patients at high risk for worse outcomes including T2D, but a formal risk prediction analyses is warranted. Assessment of HGS is quick and low-cost, hence studies are needed to assess its suitability in risk assessment. Furthermore, though there is considerable evidence that physical activity can prevent or delay T2D,[56,57] the use of interventions which build muscle strength such as resistance training, could be evaluated as potential preventive strategies for T2D.

Several strengths of this review deserve consideration. A comprehensive search of the major databases was conducted to identify all published observational cohort studies conducted on the topic, hence there was enhanced power to reliably assess the nature and magnitude of the prospective association between HGS and T2D risk. Reported risk estimates were transformed to consistent comparisons using standard and well-established reliable methods and this enhanced the pooling process for easy interpretation. We quantified and explored for sources of heterogeneity using stratification by several study level characteristics and estimating prediction intervals. Some important limitations included the inability to transform some of the risk estimates to extreme tertiles, hence comparisons could only be made between the maximum versus minimum value of HGS. However, we have demonstrated in a previous study that

pooled results from untransformed data of extreme categories are not very different from results based on transformed data.[35] There was variation in HGS assessment methods across studies, hence the pooled estimate may be biased. In a comprehensive review of the measurement of grip strength in clinical and epidemiological, Roberts and colleagues reported considerable variation in methods of assessing grip strength hence making comparison between studies difficult.[58] The authors called for the use of a standardised approach by studies. The Jamar hand dynamometer is the most widely used tool and testing procedures should follow the American Society of Hand Therapists (ASHT) recommendations[59] or the Southampton protocol.[58] Definition of T2D outcomes did not vary much across studies, given that majority of studies employed ADA diagnostic criteria. Handgrip strength values were based on baseline assessments, hence the potential for regression dilution bias and hence possibly underestimating the associations. Finally, there was substantial heterogeneity between contributing studies and the estimated 95% prediction intervals of the pooled estimate for the association between HGS and T2D risk contained values below and above 1, and so although on average there was evidence of an association, this may not always be the case in other studies. Heterogeneity was partly explained by the study size; there could be other sources of variation such as participants, HGS assessment, outcome ascertainment, and in the results, which could not be explored because of inability to access individual level data. In addition, the presence of substantial heterogeneity makes pooling of data somewhat controversial, but we conducted subgroup analyses and made great efforts to identify the possible sources of heterogeneity. In light of these limitations, the findings should be interpreted with caution. To address the issues with variability of HGS assessments, consistent adjustment for confounding, exploration of dose-response relationships and assessment of heterogeneity, we propose an individual participant data meta-analysis of these cohort studies.

CONCLUSION

Pooled analysis of observational cohort studies suggests that HGS may be a risk indicator for T2D in the general population. The role of utilizing HGS measurements as an easily available clinical measure in the prevention of T2D warrants further investigation.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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COMPETING INTERESTS

The authors declare that they have no competing interests in this section.

AUTHORSHIP

S.K.K. designed study; conducted data collection; data analyses; interpretation; drafting of the manuscript; and critical revision of the manuscript for intellectual content. N.M.I. contributed to data collection and critical revision of the manuscript for intellectual content. H.K. designed study; contributed to interpretation; and critical revision of the manuscript for intellectual content. J.A.L. designed study;

contributed to interpretation; and critical revision of the manuscript for intellectual content.

S.K.K. is the guarantor of this work, and, as such, had full access to all the data in the study and takes/ responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

FIGURE 1 Study selection process

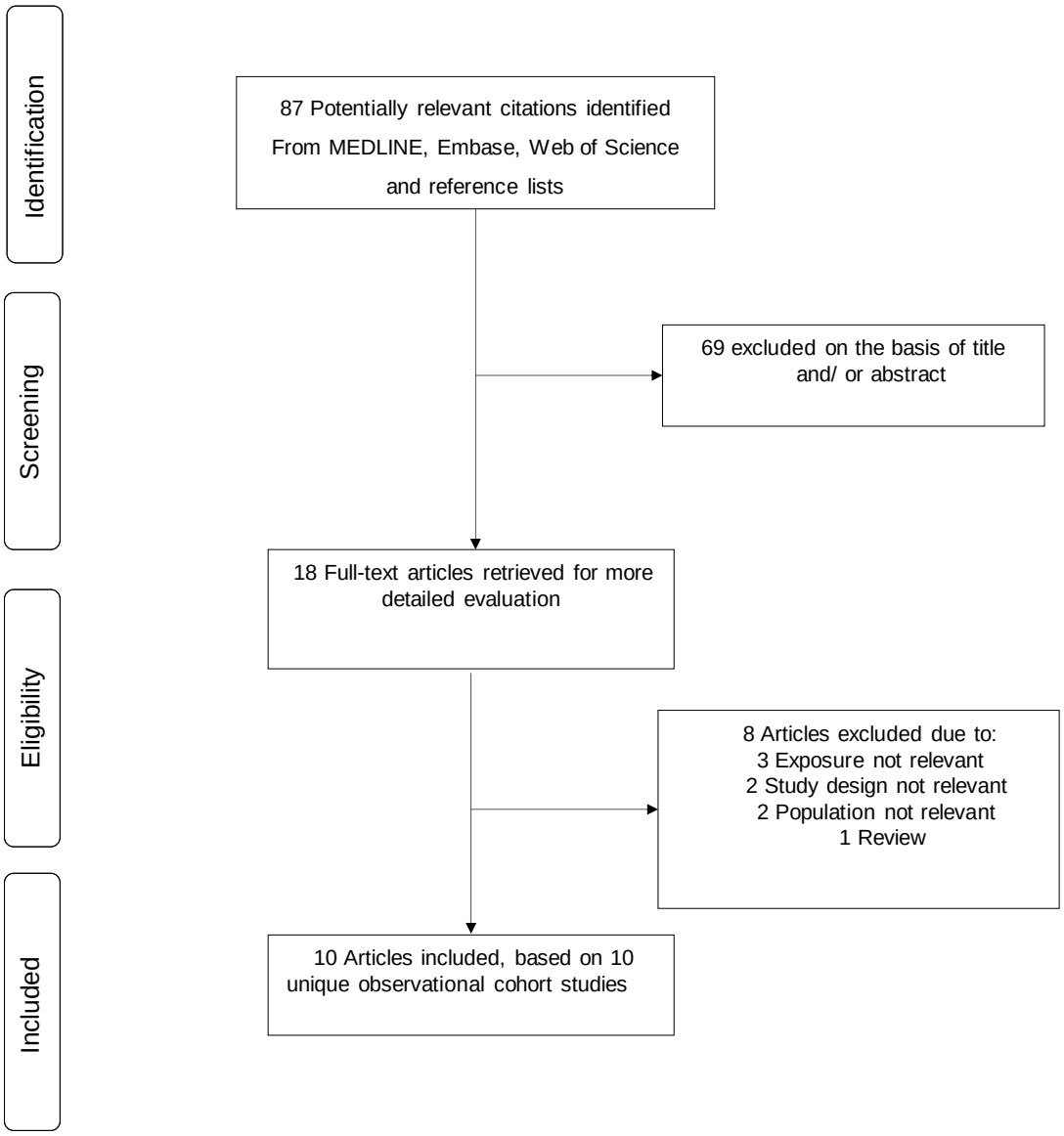
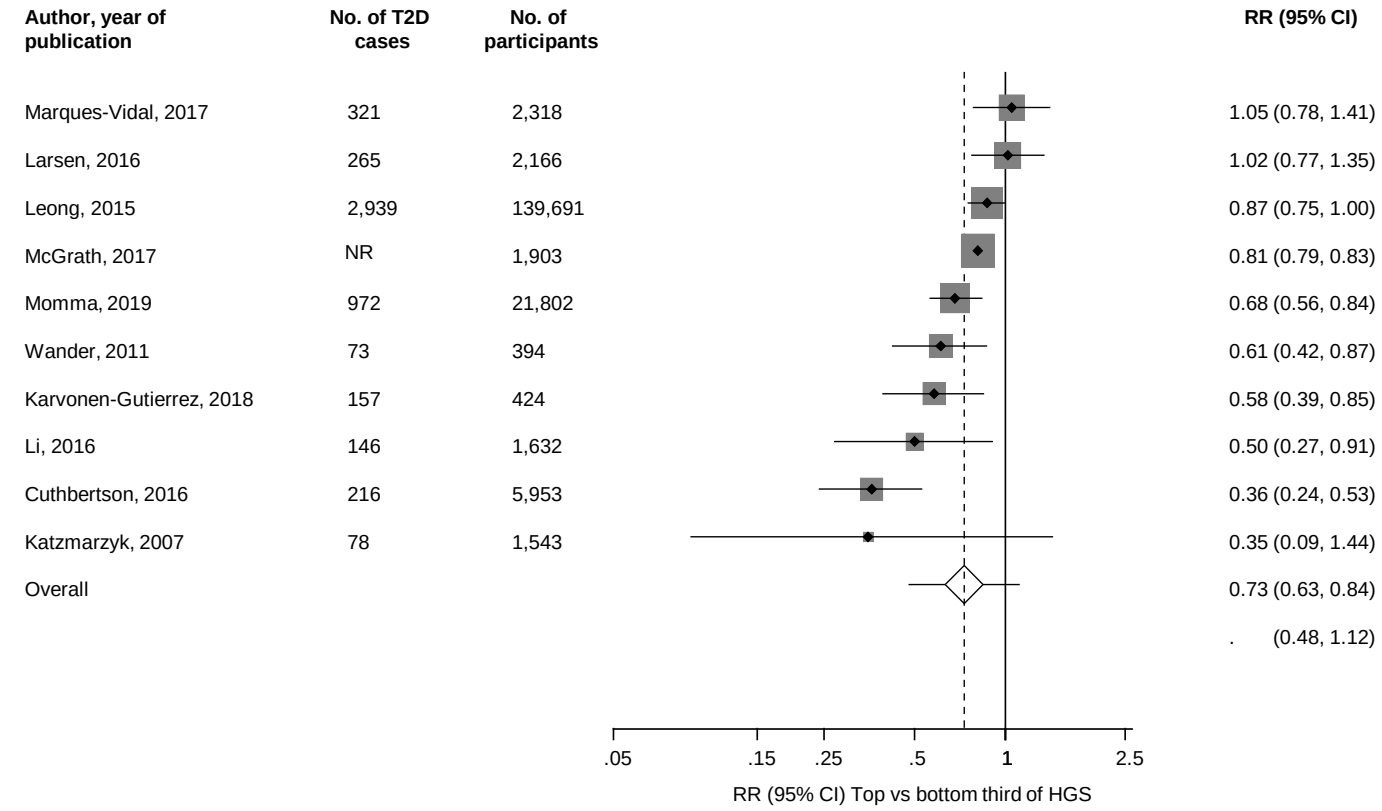
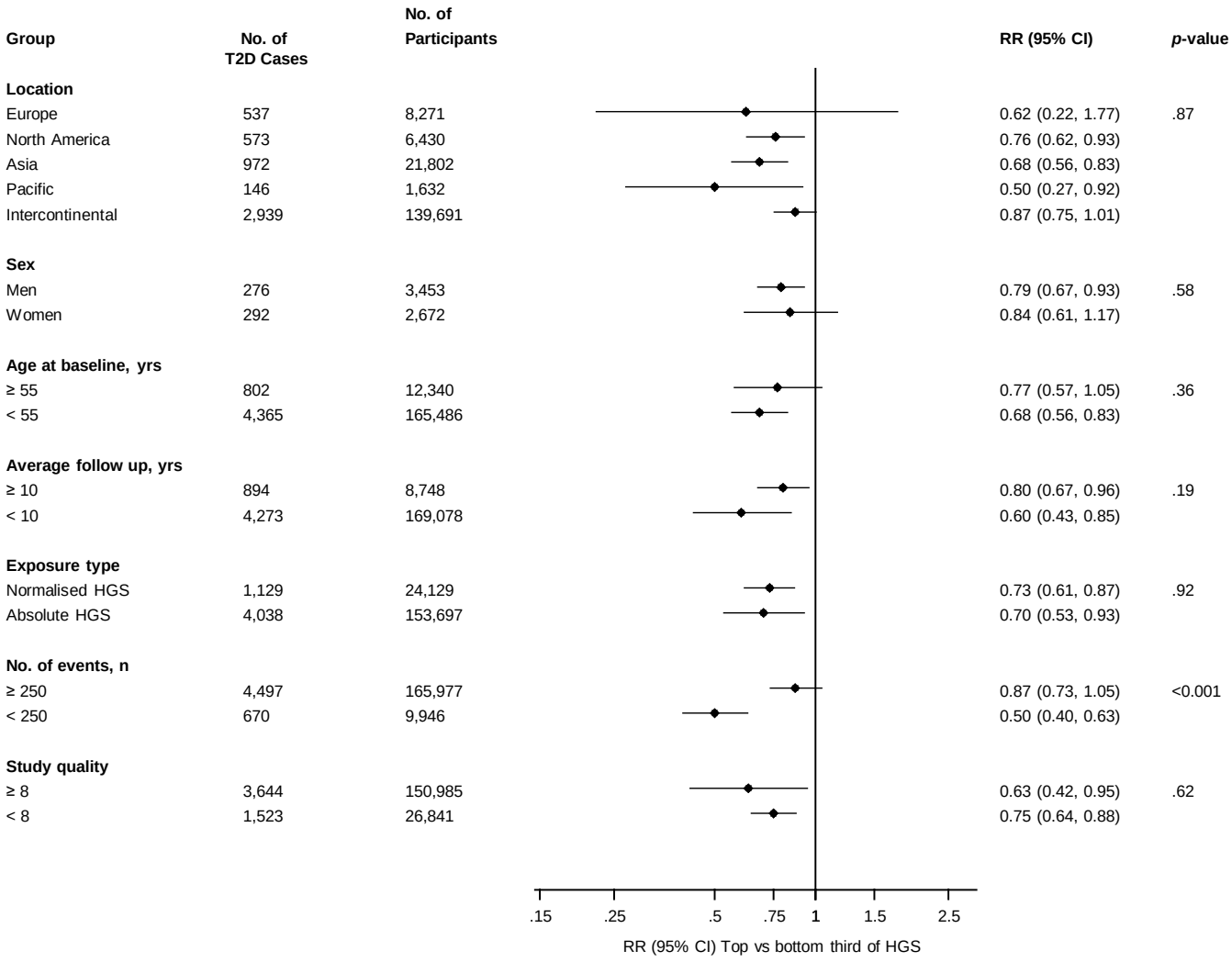


FIGURE 2 Association between handgrip strength and risk of T2D in prospective cohort studies



The summary estimates presented were calculated using random effects models; relative risks are reported comparing extreme tertiles of handgrip strength; size of data markers is proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); HGS, handgrip strength; NR, not reported; RR, relative risk

FIGURE 3 Association between handgrip strength and risk of T2D by several study-level characteristics



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars); HGS, handgrip strength; RR, relative risk; *, *p*-value for meta-regression

Table 1. Baseline characteristics of included studies (2007-2019)

Author, year of publication	Study name	Country	Baseline year	Mean/median age (yrs)	Male (%)	Follow-up (yrs)	HGS exposure values	No. of participants	No. of T2D cases	Confounders adjusted for
Katzmarzyk, 2007	Canadian PALS	Canada	1988	37.2	45.9	15.5	Absolute	1,543	78	Age, sex, smoking status, alcohol consumption and parental history of DM
Wander, 2011	Japanese-American Community Diabetes Study	USA	1983-1991	51.9	53	10.0	Absolute	394	73	Age, sex, family history, and BMI
Leong, 2015	PURE	17 countries	2003-2010	50.0	42	4.0	Absolute	139,691	2,939	Age; sex; education level; employment status; physical activity level; tobacco and alcohol use; daily dietary energy intake; proportion of caloric intake from protein; self-reported hypertension, DM, HF, CAD, and COPD; and self-reported prior stroke or cancer; BMI and WHR
Cuthbertson, 2016	ELSA	UK	2004-2005	63.0	45	6.0	Absolute	5,953	216	Age, sex, physical activity, smoking, alcohol, depressive symptoms and prevalent CVD
Li, 2016	MAILES	Australia	2002-2006; 2007-2010	54.1	100	5.0	Absolute	1,632	146	Age, income, cohort, WC, FPG, physical activity, hypertension, TG and family history of DM, and whole-body lean mass
Larsen, 2016	Health ABC	USA	1997-1998	74.0	48	11.3	Absolute	2,166	265	Age, race, clinical site, physical activity, smoking, lipids, hypertension, BMI, visceral fat, and total body fat
Marques-Vidal, 2017	CoLaus	Switzerland	2003-2006	60.2		10.7	Absolute	2,318	321	Age, maternal and paternal diabetes, height, WC, alcohol consumption, hypertension, HR, glucose, TG, HDL-C and uric acid
McGrath, 2017	HEPESE	USA	1993-1994	73.3	42.1	19.0	Normalised*	1,903	NR	Education level, employment status, marital status, IADL disability, interview language, and obesity
Karvonen-Gutierrez, 2018	Michigan SWAN	USA	1996	46.4	0	16.0	Normalised *	424	157	Age, race/ethnicity, difficulty paying for basics, smoking status, and WHR
Momma, 2019	Niigata Wellness Study	Japan	2001-2002	50.0	69.5	5.0	Normalised *	21,802	972	Age, sex, smoking status, drinking status, breakfast skipping, hypertension, dyslipidemia, and BMI

*, are weight normalised values

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HGS, handgrip strength; HR, heart rate; IADL, instrumental activities of daily living; NR, not reported; TG, triglyceride; WC, waist circumference; WHR, waist-to-hip ratio

Study Abbreviations: ABC, Health, Aging and Body Composition; ELSA, English Longitudinal Study of Ageing; HEPESE, Hispanic Established Population for the Epidemiological Study of the Elderly; MAILES, Men Androgens Inflammation Lifestyle Environment and Stress; PALS, Physical Activity Longitudinal Study; PURE, Prospective Urban-Rural Epidemiology; SWAN, Study of Women's Health Across the Nation

Table 2. Handgrip strength assessment and definition of incident T2D outcomes (2007-2019)

Author, year of publication	HGS tool; assessment method	Definition of T2D
Katzmarzyk, 2007	Stoelting adjustable dynamometer; the maximum grip strengths of three trials for each hand were summed to provide a single measure of grip strength	Self-reported physician diagnosis
Wander, 2011	Harpenden R dynamometer (British Indicators Ltd, St Albans, England); measured three times on the dominant hand (reset to 0 each time); the value entered was the average of the two highest values	FPG ≥ 126 mg/dl and/or 2-hr glucose ≥ 200 mg/dl or use of diabetes medication.
Leong, 2015	Jamar dynamometer; three measurements were made from the participant's non-dominant hand. During the course of the study, the protocol was amended so that three measurements were made from both hands of each participant. We used only the maximum values obtained from each hand	NR
Cuthbertson, 2016	NR; assessed in the dominant hand and used the average of three measurements	Self-reported physician diagnosis based on a FPG ≥7.0 mmol/l
Li, 2016	Jamar analog ((Lafayette Instrument Company, Lafayette, Indiana, USA) or Smedley ((Stoelting Corporation, Wood Dale, Illinois, USA) analog dynamometer; mean of three measurements used	Previous doctor diagnosis, diabetes medication use, FPG ≥7·0 mmol/L (≥126 mg/dl), or HbA1c ≥6·5% (48 mmol/mol).
Larsen, 2016	Isometric dynamometer (Jaymar; JLW Instruments, Chicago, IL); Two trials were performed for each hand; the mean of all four readings was used as the grip strength measure	FPG ≥126 mg/dL, and/or reporting a physician's diagnosis of diabetes and/or use of hypoglycaemic medication at the follow-up examination
Marques-Vidal, 2017	Baseline® Hydraulic Hand Dynamometer (Fabrication Enterprises Inc, Elmsford, NY, USA); used American Society of Hand Therapists's guidelines; three measurements were performed consecutively with the right hand and maximum value used	FPG ≥7.0 mmol/l; HbA1c levels (≥6.5% or 48 mmol/mol).
McGrath, 2017	Hand-held dynamometer (Jamar Hydraulic Dynamometer; J.A. Corp); While seated, participants performed the test with their dominant hand, exhaling while squeezing; wo trials were performed, and the higher of the two measurements divided by body weight was used	Self-reported physician diagnosis
Karvonen-Gutierrez, 2018	Baseline® hydraulic hand dynamometer; measured separately three times on both hands at each study visit while the participant was seated with her elbow bent at a 90° angle; maximum grip strength used value used and divided by body weight	(1) Self-reported doctor's diagnosis of diabetes; (2) self-reported use of anti-diabetic medications (oral medications or insulin) or (3) FPG ≥126 mg/dl orHbA1c ≥6.5%.
Momma, 2019	Grip strength dynamometer (T.K.K. 5401; Takei Scientific Instruments Co., Ltd, Niigata, Japan); grip strength was measured once for each hand alternately with individuals in standing position; the highest value was used and divided by body weight	FPG ≥126 mg=dL (7.0 mmol=L), HbA1c ≥48 mmol=mol (6.5%), or a self-reported history of previously diagnosed diabetes or current medication for diabetes

FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HGS, handgrip strength; NR, not reported; T2D, type 2 diabetes

Supplementary Material

Table S1	PRISMA checklist
Table S2	MOOSE checklist
Table S3	Literature search strategy
Table S4	Methodological quality of studies using NOS criteria
Figure S1	Relative risks on exclusion of a study one at a time
Figure S2	Assessment of small study effects by funnel plot and Egger's regression symmetry test

Table S1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Table S2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Results, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Table 1, Figure 3
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Results; Figure 3; Figure S1
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Funding section

Table S2. MOOSE checklist

Handgrip strength – a risk indicator for type 2 diabetes: systematic review and meta-analysis of observational cohort studies

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Evidence on the association between handgrip strength and type 2 diabetes (T2D) is inconsistent
√	Hypothesis statement	Handgrip strength is associated with T2D
√	Description of study outcomes	Type 2 diabetes
√	Type of exposure	Handgrip strength
√	Type of study designs used	Prospective cohort studies
√	Study population	Adult general populations with assessment of handgrip strength at study entry
Reporting of search strategy should include		
√	Qualifications of searchers	Setor K. Kunutsor, PhD; Nzechukwu Isiozor, MD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 21 April 2020 The detailed search strategy can be found in Appendix 3
√	Databases and registries searched	MEDLINE, Embase, Web of Science
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote X9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	None
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Heterogeneity of the studies was quantified with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity and explored using meta-regression and stratified analyses
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods. We performed random effects meta-analysis with Stata 15.
√	Provision of appropriate tables and graphics	Table 1; Figures 1-3; Figure S1
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Sensitivity analysis was conducted to assess the influence of some large studies and low-quality studies on the pooled estimate.

√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. The systematic review is limited in scope, as it involves published data. Individual participant data is needed. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend individual participant data meta-analysis
√	Disclosure of funding source	In "Acknowledgement" section

Table S3. Literature search strategy

Relevant studies, published from inception to 21 April 2020 (date last searched), were identified through electronic searches using MEDLINE and Embase databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and cited reference search in Web of Science.

Database: Ovid MEDLINE(R) <1946 to present>
Search Strategy:
---
1 handgrip strength.mp. (2703)
2 grip strength.mp. (10948)
3 exp Muscle Strength/ (33011)
4 muscular strength.mp. (3294)
5 exp Diabetes Mellitus, Type 2/ (130550)
6 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. (2565855)
7 1 or 2 or 3 or 4 (42248)
8 5 and 6 and 7 (58)
9 limit 8 to humans (58)
****

Each part was specifically translated for searching the other databases (Embase and Web of Science)

Table S4. Methodological quality of studies using NOS criteria

Author, year of publication	Selection	Comparability	Outcome	Total score
Katzmarzyk, 2007	4	2	2	8
Wander, 2011	3	1	3	7
Leong, 2015	4	2	3	9
Cuthbertson, 2016	4	2	2	8
Li, 2016	4	2	3	9
Larsen, 2016	3	2	3	8
Marques-Vidal, 2017	3	2	2	7
McGrath, 2017	3	1	3	7
Karvonen-Gutierrez, 2018	3	2	2	7
Momma, 2019	3	2	2	7

Figure S1. Relative risks on exclusion of a study one at a time

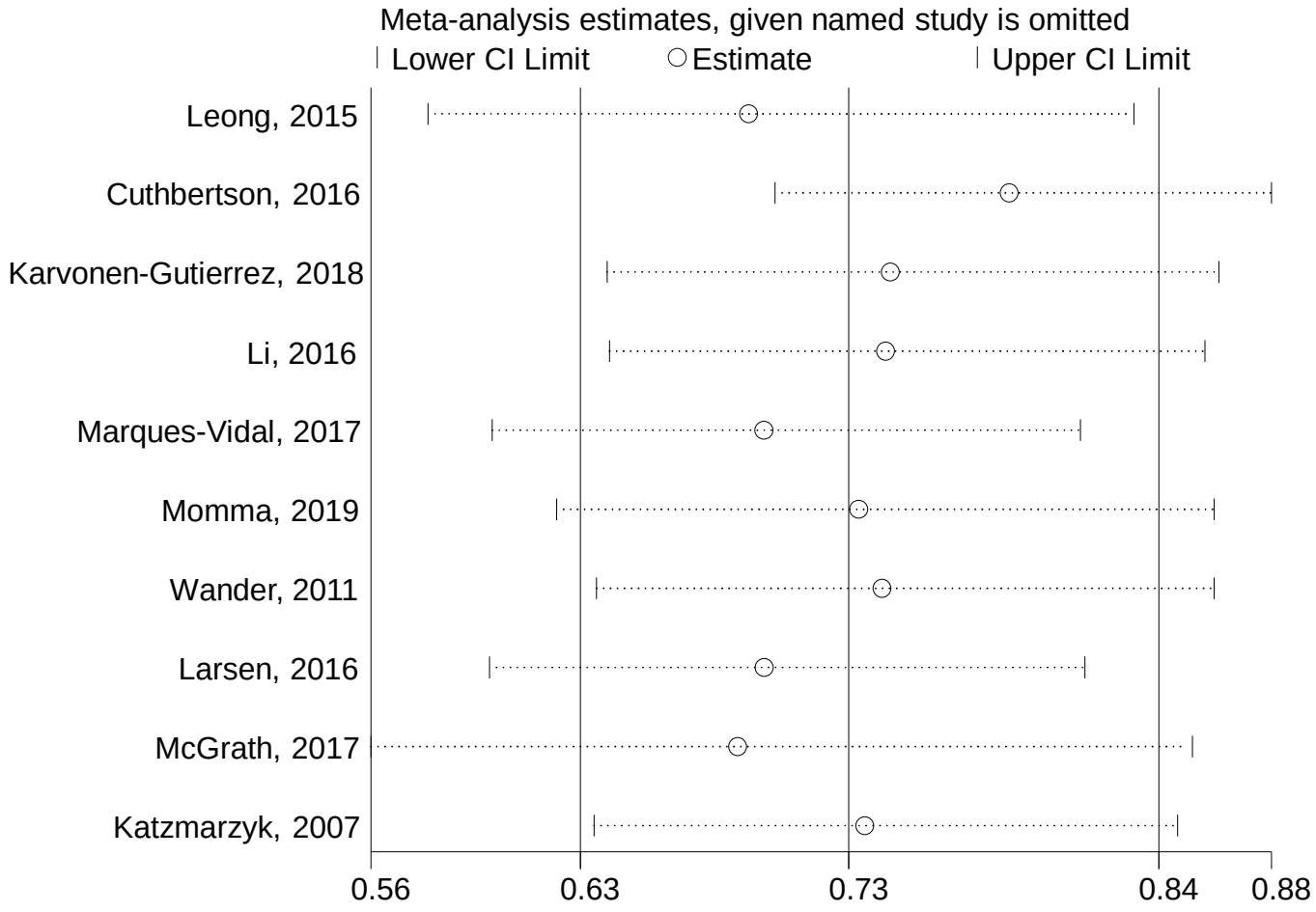


Figure S2. Assessment of small study effects by funnel plot and Egger's regression symmetry test